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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,063	08/22/2003	Martin H. Teicher	04843/113003	8435
21559	7590	11/29/2005	EXAMINER	
CLARK & ELBING LLP			CORDERO GARCIA, MARCELA M	
101 FEDERAL STREET			ART UNIT	
BOSTON, MA 02110			PAPER NUMBER	

1654

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/646,063

Applicant(s)

TEICHER ET AL.

Examiner

Marcela M. Cordero Garcia

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12, 13, 15, 19-23 and 29-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12, 13, 15, 19-23 and 29-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is in response to the reply received on October 3, 2005.

Claims 12-15, 19-28 and new claims 29-30 are pending in the application.

Any rejection from the previous office action, which is not restated here, is withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The species polyguanidyl conjugate of Example 3, page 30 of the specification, for the treatment of rheumatoid arthritis was searched and found free of the prior art (see previous Office Action of March 31, 2005).

The examiner elected a new species: dextran-methylprednisolone succinate for the treatment of organ/tissue transplant rejection.

Claims 12, 13, 15, 19, 20, 21, 22 and 23 and new claims 29-30 are readable thereon.

Claims 12, 13, 15, 19, 20, 21, 22 and 23 and new claims 29-30 are presented for examination on the merits.

Claim Rejections - 35 USC § 102

Claims 12, 13, 15, 19, 20-23 and 29-30 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (J Pharm Sci, 2001).

Zhang et al. teach a method of treating an autoimmune or inflammatory condition in a mammal, said method comprising administering to said mammal a corticosteroid conjugate comprising a corticosteroid attached to a group that is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons in an amount effective to treat said condition, wherein said corticosteroid conjugate has anti-inflammatory activity in vivo and reduced activity in the central nervous system in comparison to said corticosteroid without said group and wherein said corticosteroid conjugate is resistant to in vivo cleavage (see entire document, e.g., abstract and column 1, paragraph 1, page 2079, Scheme I, page 2079 and pages 2085-2086).

Therefore, the reference is deemed to anticipate the instant claims above.

Applicant argues that the newly recited limitation that “the corticosteroid conjugate is resistant to *in vivo* cleavage” distinguishes now the invention from the prior art cited. Applicant argues that Zhang teaches the use of a corticosteroid-dextran prodrug conjugate for the treatment of inflammatory conditions. See for example, Zhang at page 2079, right column, which recites:

Dextran-methylprednisolone succinate (DMP), a conjugate of MP and dextran containing two ester bonds, was synthesized using succinic acid as a linker between the polymer and MP (Scheme I). Hydrolysis studies showed that at physiological pH, DMP is slowly hydrolyzed at both ester bonds (Scheme I), resulting in the formation of MP and methylprednisolone succinate (MPS), the latter being subsequently converted to MP.

Applicant argues that the corticosteroid conjugate of Zhang is designed to be cleaved in vivo. The purpose of the Zhang's conjugate is to target the corticosteroid to the liver and spleen. Once delivered to the targeted site, the conjugate is cleaved,

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releasing unconjugated corticosteroid at the site. See, e.g., Zhang in the abstract, which recites:

As for tissue distribution, the conjugate delivered the steroid primarily to the spleen and liver as indicated by 19- and 3- fold increases, respectively, in the tissue/plasma area under the curve (AUC) ratios of the steroid. On the other hand, the tissue/plasma AUC ratios of the prodrug in other organs were negligible. Active MP was released from DMP slowly in the spleen and liver, and AUCs of the regenerated MP in the tissues were 55- and 4.8- fold, respectively, higher than those after the administration of the parent drug.

In contrast to Zhang, Applicant argues, the claims of the present invention are directed to the use of corticosteroid conjugates that are resistant to *in vivo* cleavage.

See, for example, the specification at page 21, lines 15-22, which recite:

The corticosteroid conjugates of the present invention are designed to largely remain intact *in vivo*, resisting cleavage by intracellular and extracellular enzymes (e.g., amidases, esterases and phosphatases). Any *in vivo* cleavage of the corticosteroid conjugate produces the parent steroid, resulting in the unnecessary and potentially harmful exposure of the central nervous system to this corticosteroid. Thus, the corticosteroid conjugates of the invention are not prodrugs, but are therapeutically active in their conjugated form, resulting in an improved therapeutic index relative to their parent, unconjugated, corticosteroid.

Applicant argues that all pending claims are directed to corticosteroid conjugates that are resistant to *in vivo* cleavage. Because Zhang teaches the use of corticosteroid conjugate prodrugs which undergo cleavage *in vivo*, Zhang is not relevant to the novelty of the pending claims.

Applicant's arguments have been carefully considered but not deemed persuasive by Examiner for the reasons of record and because:

In the specification, at page 10, lines 3-5, Applicant writes:

By "resistant to *in vivo* cleavage" is meant that, *in vivo*, less than 30, 20, 10, 5, 2, or 1 percent of the administered drug is cleaved, separating the corticosteroid from the charged group or the bulky group, prior to excretion.

Please note that Applicant's definition of "resistant to *in vivo* cleavage" within the disclosure of the instant application allows for hydrolysis of up to 30% of the conjugate.

Zhang et al teach that conjugates of dextran and methylprednisolone slowly hydrolyze and have a much longer half-life than the unconjugated methylprednisolone, as corroborated by the absence of methylprednisolone in plasma after injection of the conjugate. (See, e.g., page 2085, column 1, lines 16-39 and Figure 3).

Please also note that the method taught by Zhang teaches conjugates reciting all structural elements of those used within the method instantly claimed, therefore, any functional effects of the conjugates such as "resistance to in vivo cleavage" are deemed inherent to such molecular structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 13, 15, 19, 20-23 and 29-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (J Pharm Sci, 2001).

Zhang et al. beneficially teach a method of treating an autoimmune or inflammatory condition in a mammal, said method comprising administering to said mammal a corticosteroid conjugate comprising a corticosteroid attached to a group that is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons in an amount effective to treat said condition, wherein said corticosteroid conjugate has anti-inflammatory activity in vivo and reduced activity in the central nervous system in comparison to said corticosteroid without said group and wherein said corticosteroid conjugate is resistant to in vivo cleavage (see e.g., Scheme I, abstract and column 1, paragraph 1, page 2079, and pages 2085-2086).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to adjust particular conventional working conditions within such a therapeutic method (e.g., using different modes of administration) based upon the overall beneficial teachings provided by Zhang et al. These types of adjustments are deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Applicant traverses the rejection and argues that, as amended, all of the claims are directed to conjugates that are resistant to in vivo cleavage. Zhang teaches only the use of cleavable prodrug corticosteroid conjugates, i.e., conjugates that are not resistant to in vivo cleavage. All of the pending claims are nonobvious over Zhang because

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Zhang does not teach or suggest the use of corticosteroid conjugates resistant to *in vivo* cleavage for the treatment of autoimmune or inflammatory conditions.

Applicant's arguments have been carefully considered by Examiner, but not deemed persuasive for the reasons of record and because:

In the specification, at page 10, lines 3-5, Applicant writes:

By "resistant to *in vivo* cleavage" is meant that, *in vivo*, less than 30, 20, 10, 5, 2, or 1 percent of the administered drug is cleaved, separating the corticosteroid from the charged group or the bulky group, prior to excretion.

Please note that Applicant's definition of "resistant to *in vivo* cleavage" within the disclosure of the instant application allows for hydrolysis of up to 30% of the conjugate.

Zhang et al teach that conjugates of dextran and methylprednisolone slowly hydrolyze and have a much longer half-life than the unconjugated methylprednisolone, as corroborated by the absence of methylprednisolone in plasma after injection of the conjugate. (See, e.g., page 2085, column 1, lines 16-39 and Figure 3).

Please also note that the conjugate by Zhang has all elements claimed by the instant invention, therefore, any functional effects such as "resistance to *in vivo* cleavage" are deemed intrinsic to such molecular structure.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

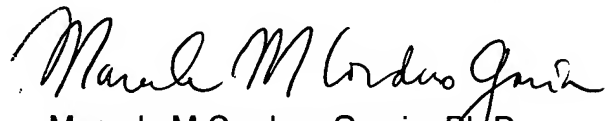
No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Marcela M Cordero Garcia, Ph.D.
Patent Examiner
Art Unit 1654

MMCG 11/05



CHRISTOPHER R. TATE
PRIMARY EXAMINER